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NEWS	1		Web Page for STN Seminar Schedule - N. America
NEWS	2	AUG 15	CAOLD to be discontinued on December 31, 2008
NEWS	3	OCT 07	EPFULL enhanced with full implementation of EPC2000
NEWS	4	OCT 07	Multiple databases enhanced for more flexible patent number searching
NEWS	5	OCT 22	Current-awareness alert (SDI) setup and editing enhanced
NEWS	6	OCT 22	WPIDS, WPINDEX, and WPIX enhanced with Canadian PCT Applications
NEWS	7	OCT 24	CHEMLIST enhanced with intermediate list of pre-registered REACH substances
NEWS	8	NOV 21	CAS patent coverage to include exemplified prophetic substances identified in English-, French-, German-, and Japanese-language basic patents from 2004-present
NEWS	9	NOV 26	MARPAT enhanced with FSORT command
NEWS	10	NOV 26	MEDLINE year-end processing temporarily halts availability of new fully-indexed citations
NEWS	11	NOV 26	CHEMSAFE now available on STN Easy
NEWS	12	NOV 26	Two new SET commands increase convenience of STN searching
NEWS	13	DEC 01	ChemPort single article sales feature unavailable
NEWS	14	DEC 12	GBFULL now offers single source for full-text coverage of complete UK patent families
NEWS	15	DEC 17	Fifty-one pharmaceutical ingredients added to PS
NEWS	16	JAN 06	The retention policy for unread STNmail messages will change in 2009 for STN-Columbus and STN-Tokyo

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AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
NEWS LOGIN Welcome Banner and News Items
NEWS IPC8 For general information regarding STN implementation of IPC 8

Enter NEWS followed by the item number or name to see news on that specific topic.

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=> s (S6K or (S6 kinase)) (6A) (ribosome or ribosomal)
L1        4486 (S6K OR (S6 KINASE)) (6A) (RIBOSOME OR RIBOSOMAL)

=> s (S6K or (S6 kinase)) (8A) (fat or lipid or obesity or obese or overweight or
adipose or fatty or glycerol)
L2          79 (S6K OR (S6 KINASE)) (8A) (FAT OR LIPID OR OBESITY OR OBESE OR
               OVERWEIGHT OR ADIPOSE OR FATTY OR GLYCEROL)

=> s l1 and l2
L3          32 L1 AND L2

=> duplicate
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ENTER L# LIST OR (END):l3
DUPLICATE PREFERENCE IS 'MEDLINE, EMBASE, BIOSIS, CAPLUS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L3
L4           19 DUPLICATE REMOVE L3 (13 DUPLICATES REMOVED)

=> d l4 1-19 bib ab

L4   ANSWER 1 OF 19     MEDLINE on STN                  DUPLICATE 1
AN   2007643363     MEDLINE
DN   PubMed ID: 17967350
TI   Effect of insulin and 20-hydroxyecdysone in the fat body of the yellow
     fever mosquito, Aedes aegypti.
AU   Roy Saurabh G; Hansen Immo A; Raikhel Alexander S
CS   Graduate Program in Cell, Molecular and Developmental Biology, University
     of California, Riverside, CA 92521, USA.
NC   R37 AI024716-20 (United States NIAID)
     R37 AI24716 (United States NIAID)
SO   Insect biochemistry and molecular biology, (2007 Dec) Vol. 37, No. 12, pp.
     1317-26.  Electronic Publication: 2007-09-01.
     Journal code: 9207282. ISSN: 0965-1748.
CY   England: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
     (RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA   English
FS   Priority Journals
EM   200802
ED   Entered STN: 31 Oct 2007
```

Last Updated on STN: 29 Feb 2008
Entered Medline: 28 Feb 2008

AB In mosquitoes, yolk protein precursor (YPP) gene expression is activated after a blood meal through the synergistic action of a steroid hormone and the amino acid/target of rapamycin (TOR) signaling pathway in the fat body. We investigated the role of insulin signaling in the regulation of YPP gene expression. The presence of mosquito insulin receptor (InR) and the Protein kinase B (PKB/Akt) in the adult fat body of female mosquitoes was confirmed by means of the RNA interference (RNAi). Fat bodies stimulated with insulin were able to promote the phosphorylation of ribosomal S6 Kinase, a key protein of the TOR signaling pathway. Importantly, insulin in combination with 20-hydroxyecdysone activated transcription of the YPP gene vitellogenin (Vg), and this process was sensitive to the phosphoinositide-3 kinase (PI-3k) inhibitor LY294002 as well as the TOR inhibitor rapamycin. RNAi-mediated knockdown of the mosquito InR, Akt, and TOR inhibited insulin-induced Vg gene expression as well as S6 Kinase phosphorylation in in vitro fat body culture assays.

L4 ANSWER 2 OF 19 MEDLINE on STN DUPLICATE 2
AN 2007186545 MEDLINE
DN PubMed ID: 17242159
TI Phospholipase D2-derived phosphatidic acid binds to and activates ribosomal p70 S6 kinase independently of mTOR.
AU Lehman Nicholas; Ledford Bill; Di Fulvio Mauricio; Frondorf Kathleen; McPhail Linda C; Gomez-Cambronero Julian
CS Cell Biology and Physiology, Wright State University, School of Medicine, 3640 Colonel Glenn Hwy., Dayton, Ohio 45435, USA.
NC AI22564 (United States NIAID)
HL056653 (United States NHLBI)
SO The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2007 Apr) Vol. 21, No. 4, pp. 1075-87. Electronic Publication: 2007-01-22.
Journal code: 8804484. E-ISSN: 1530-6860.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
LA English
FS Priority Journals
EM 200705
ED Entered STN: 29 Mar 2007
Last Updated on STN: 18 May 2007
Entered Medline: 17 May 2007

AB The product of phospholipase D (PLD) enzymatic action in cell membranes, phosphatidic acid (PA), regulates kinases implicated in NADPH oxidase activation, as well as the mammalian target of rapamycin (mTOR) kinase. However, other protein targets for this lipid second messenger must exist in order to explain other key PA-mediated cellular functions. In this study, PA was found to specifically and saturably bind to and activate recombinant and immunoprecipitated endogenous ribosomal S6 kinase (S6K) with a stoichiometry of 94:1 lipid/protein. Polyphosphoinositides PI4-P and PI4,5P2 and cardiolipin could also bind to and activate S6K, albeit with different kinetics. Conversely, PA with at least one acyl side chain saturated (10:0) was ineffective in binding or activating the enzyme. Transfection of COS-7 cells with a wild-type myc-(pcDNA)-PLD2 construct resulted in high PLD activity, concomitantly with an increase in ribosomal p70S6K enzyme activity and phosphorylation in T389 and T421/S424 as well as phosphorylation of p70S6K's natural substrate S6 protein in S235/S236. Overexpression of a lipase inactive mutant (K758R), however, failed to induce an increase in both PLD and S6K activity or phosphorylation,

indicating that the enzymatic activity of PLD2 (i.e., synthesis of PA) must be present to affect S6K. Neither inhibiting mTOR kinase activity with rapamycin nor silencing mTOR gene expression altered the augmentative effect of PLD2 exerted on p70S6K activity. This finding indicates that PA binds to and activates p70S6K, even in the absence of mTOR. Lastly, COS-7 transfection with PLD2 changed the pattern of subcellular expression, and a colocalization of S6K and PLD2 was observed by immunofluorescence microscopy. These results show for the first time a direct (mTOR-independent) participation of PLD in the p70S6K pathway and implicate PA as a nexus that brings together cell phospholipases and kinases.

L4 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2007:167941 CAPLUS
DN 146:267004
TI Elevated sensitivity to diet-induced obesity and insulin resistance in mice lacking 4E-BP1 and 4E-BP2
AU Le Bacquer, Olivier; Petroulakis, Emmanuel; Paglialunga, Sabina; Poulin, Francis; Richard, Denis; Cianflone, Katherine; Sonenberg, Nahum
CS Department of Biochemistry, McGill University, Montreal, QC, Can.
SO Journal of Clinical Investigation (2007), 117(2), 387-396
CODEN: JCINAO; ISSN: 0021-9738
PB American Society for Clinical Investigation
DT Journal
LA English
AB The most common pathol. associated with obesity is insulin resistance, which results in the onset of type 2 diabetes mellitus. Several studies have implicated the mammalian target of rapamycin (mTOR) signaling pathway in obesity. Eukaryotic translation initiation factor 4E-binding (eIF4E-binding) proteins (4E-BPs), which repress translation by binding to eIF4E, are downstream effectors of mTOR. The authors report that the combined disruption of 4E-BP1 and 4E-BP2 in mice increased their sensitivity to diet-induced obesity. Increased adiposity was explained at least in part by accelerated adipogenesis driven by increased expression of CCAAT/enhancer-binding protein δ (C/EBPδ), C/EBPα, and PPARγ coupled with reduced energy expenditure, reduced lipolysis, and greater fatty acid reesterification in the adipose tissue of 4E-BP1 and 4E-BP2 double KO mice. Increased insulin resistance in 4E-BP1 and 4E-BP2 double KO mice was associated with increased ribosomal protein S6 kinase (S6K) activity and impairment of Akt signaling in muscle, liver, and adipose tissue. These data clearly demonstrate the role of 4E-BPs as a metabolic brake in the development of obesity and reinforce the idea that deregulated mTOR signaling is associated with the development of the metabolic syndrome.
RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2008:514952 CAPLUS
DN 149:303897
TI Fatty acid transport in adipocytes and the development of insulin resistance
AU Lobo, Sandra; Bernlohr, David A.
CS Department of Biochemistry, Molecular Biology and Biophysics, The University of Minnesota, Minneapolis, MN, 55455, USA
SO Novartis Foundation Symposium (2007), 286(Fatty Acids and Lipotoxicity in Obesity and Diabetes), 113-126
CODEN: NFSYF7; ISSN: 1528-2511
PB John Wiley & Sons Ltd.
DT Journal; General Review

LA English
AB A review. Fatty acid influx into adipocytes is a complex multifactorial process driven by biochem. and biophys. processes linking transmembrane flux to the ATP-dependent esterification of fatty acids. Adipocyte proteins implicated in free fatty acid (FFA) influx include CD36 functioning as a general lipid receptor, caveolin 1 functioning as a component of an endocytotic/exocytotic vesicular cycle and the acyl CoA synthetases (FATP1, ACSL1) catalyzing esterification of lipids producing acyl CoAs. In adipocytes, CD36, ACSL1 and FATP1 translocate from intracellular sites to the plasma membrane in response to insulin thereby positioning these key proteins to facilitate FFA esterification. Lentiviral delivery of shRNA targeting FATP1 in 3T3-L1 adipocytes results in a complete loss of insulin-stimulated FFA uptake, decreased accumulation of TAG/DAG/MAG and potentiated insulin-stimulated 2-deoxyglucose uptake. Increased insulin-stimulated hexose uptake in FATP1 knockdown adipocytes is correlated with increased tyrosine phosphorylation and abundance of IRS1 protein. Evaluation of the lipid activated serine kinases implicated in insulin signalling reveals that S6K and JNK1 were not altered in abundance or phosphorylation in FATP1 knockdown adipocytes but that the phosphorylation of PKCθ and abundance of IKKα/β were significantly reduced. These results suggest lipid droplet pools in the adipocyte play a major role in regulating kinase cascades controlling insulin action.
RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2006:1114422 CAPLUS
DN 146:20297
TI Use of direct activation of p90 ribosomal s6 kinase 1(rsk1) by small organic compounds for prevention and treatment of diabetes, obesity and metabolic syndrome by increasing activity of amp-activated protein kinase
IN Kim, Sang Geon; Lee, Seung Jin; Park, Eun Young
PA Seoul National University Industry Foundation, S. Korea
SO Repub. Korean Kongkae Taeho Kongbo, No pp. given
CODEN: KRXXA7
DT Patent
LA Korean
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	KR 2006031952	A	20060414	KR 2004-80943	20041011
PRAI	KR 2004-80943		20041011		

AB Use of direct activation of p90 ribosomal S6 kinase 1(RSK1) by small organic compds. for prevention and treatment of diabetes, obesity and metabolic syndrome is provided to increase activity of AMP-activated protein kinase and reduce activity of p70 ribosomal S6 kinase, thus lowering blood sugar level and increasing insulin reactivity against cells. A treating agent of diabetes and complications thereof comprises the small organic compds. for direct activation of p90 ribosomal S6 kinase 1(RSK1), wherein the small organic compds. for direct activation of p90 ribosomal S6 kinase 1(RSK1) are 1,2-dithiole-3-thione and dicyclic compds. represented by formula(1) to formula(11) in which R1 and R2 are each hydrogen, C1-7-alkyl, C3-7-cycloalkyl, C1-7-haloalkyl, C1-7-alkoxy, C3-7-cycloalkoxy, C1-7-alkylthio, C3-7-cycloalkylthio, C1-7-alkenyl, C1-7-alkynyl, C1-7-alkylsulfonyl, C1-7-alkoxycarbonyl, HO-C1-7-alkyl, HS-C1-7-alkyl, hydroxyl, thiol, halogen, carboxyl, nitro, cyano, C1-7-alkylcarbonyl, C1-7-alkoxycarbonyl, C1-7-alkylcarbonyloxy, C1-7-alkylcarbonyl-C1-4-alkyl,

C1-4-alkoxy-C1-4-alkyl, C1-4-alkylthio-C1-4-alkyl, amino, C1-7-alkylamino, C1-7-alkylcarbonylamino, C1-4-alkoxy-C1-4-alkylamino, C1-4-alkylthio-C1-4-alkylamino, C1-4-alkylsulfonamino, Ph, heteroaryl, phenyl-C1-4-alkyl, heteroaryl-C1-4-alkyl, phenyl-C1-4-alkoxy-C1-4-alkyl, phenyl-C1-4-alkylthio-C1-4-alkyl, phenoxy-C1-4-alkyl, phenylthio-C1-4-alkyl, phenylcarbonylamino, phenoxy-C1-4-alkylcarbonylamino, phenyl-C1-4-alkoxy-C1-4-alkylcarbonylamino, heteroaryloxy-C1-4-alkyl, heteroarylthio-C1-4-alkyl or heteroaryl-C1-4-alkylthio-C1-4-alkyl.

L4 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2006:715143 CAPLUS
DN 145:328690
TI The adipose tissue triglyceride lipase ATGL/PNPLA2 is downregulated by insulin and TNF-α in 3T3-L1 adipocytes and is a target for transactivation by PPARγ
AU Kim, Ji Young; Tillison, Kristin; Lee, Jun-Ho; Rearick, David A.; Smas, Cynthia M.
CS Department of Biochemistry and Cancer Biology, Medical University of Ohio, Toledo, OH, USA
SO American Journal of Physiology (2006), 291(1, Pt. 1), E115-E127
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB The minimal adipose phenotype of hormone-sensitive lipase (HSL)-null mice suggested that other hormonally responsive lipase(s) were present in adipocytes. Recent studies have characterized a new adipose tissue triglyceride lipase, ATGL/PNPLA2/destnutrin/iPLA2ξ/TTS2.2 (ATGL). The authors had previously cloned a novel adipose-enriched transcript by differential screening and recently determined its identity with murine ATGL. The authors report on the regulation of ATGL by TNF-α and insulin in 3T3-L1 adipocytes and identify ATGL as a target for transcriptional activation by the key adipogenic transcription factor PPARγ. Insulin at 100 nM resulted in a marked decrease in ATGL transcript that was effectively blocked by inhibitors for PI 3-kinase and p70 ribosomal protein S6 kinase. TNF-α treatment decreased ATGL transcript in a time-dependent manner that paralleled TNF-α downregulation of PPARγ with a maximal decrease noted by 6 h. TNF-α effects on ATGL were attenuated by pretreatment with PD-98059, LY-294002, or rapamycin, suggesting involvement of the p44/42 MAP kinase, PI 3-kinase, and p70 ribosomal protein S6 kinase signals. To study transcriptional regulation of ATGL, the authors cloned 2979 bp of the murine ATGL 5'-flanking region. Compared with promoterless pGL2-Basic, the -2979/+21 ATGL luciferase construct demonstrated 120- and 40-fold increases in activity in white and brown adipocytes, resp. Luciferase reporter activities for a series of eight ATGL promoter deletions revealed that the -928/+21, -1738/+21, -1979/+21, and -2979/+21 constructs were transactivated by PPARγ. The authors' findings identify the novel lipase ATGL to be a target gene for TNF-α and insulin action in adipocytes and reveal that it is subject to transcriptional control by PPARγ-mediated signals.
RE.CNT 81 THERE ARE 81 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2005:182924 CAPLUS
DN 142:254624
TI Inhibition of S6 kinase activity for the treatment of insulin resistance
IN Auwerx, Johan; Frigerio, Francesca; Fumagalli, Stefano; Kozma, Sara;

Picard, Frederic; Sticker-Jantscheff, Melanie; Thomas, George; Um, Sung Hee; Watanabe, Mitsuhiro
PA Novartis Forschungsstiftung, Zweigniederlassung Friedrich Miescher Institute for Biomedical Research, Switz.
SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2005019829	A1	20050303	WO 2004-EP9368	20040820
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1658504	A1	20060524	EP 2004-764350	20040820
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
JP 2007503203	T	20070222	JP 2006-523617	20040820
US 20070191259	A1	20070816	US 2007-568637	20070322
PRAI US 2003-497226P	P	20030822		
WO 2004-EP9368	W	20040820		

AB The invention provides screening methods for agents effective in treating insulin resistance through specific inhibition of S6 kinase 1 activity. Also provided are methods of treating insulin resistance by administering an effective amount of an inhibitor specific for S6 kinase 1. The inhibitor may be e.g. an antibody.
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2004:355107 CAPLUS
DN 140:368702
TI Modulation of S6 kinase 1 activity for the treatment of obesity and screening for antiobesity drugs
IN Frigerio, Francesca; Fumagalli, Stefano; Kozma, Sara C.; Sticker-Jantscheff, Melanie; Thomas, George; Um, Sung Hee
PA Novartis Forschungsstiftung, Zweigniederlassung Friedrich Miescher Institute for Biomedical Research, Switz.
SO PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004035815	A1	20040429	WO 2003-EP11554	20031017
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003282035 A1 20040504 AU 2003-282035 20031017
EP 1556505 A1 20050727 EP 2003-773650 20031017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
JP 2006502744 T 20060126 JP 2005-501296 20031017
US 20070053910 A1 20070308 US 2006-531515 20060616
PRAI GB 2002-24338 A 20021018
US 2003-497227P P 20030822
WO 2003-EP11554 W 20031017

AB This invention provides screening methods for agents effective in treating obesity through specific inhibition of S6 kinase 1 activity. Also provided are methods of treating obesity by administering an effective amount of an inhibitor specific for S6 kinase 1. A double stranded RNA for use as a medicament is provided.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2003:619991 CAPLUS
DN 139:275208
TI Insulin resistance and lipodystrophy in mice lacking ribosomal S6 kinase 2
AU El-Haschimi, Karim; Dufresne, Scott D.; Hirshman, Michael F.; Flier, Jeffrey S.; Goodyear, Laurie J.; Bjorbaek, Christian
CS Beth Israel Deaconess Medical Center, Boston, MA, USA
SO Diabetes (2003), 52(6), 1340-1346
CODEN: DIAEAZ; ISSN: 0012-1797
PB American Diabetes Association
DT Journal
LA English
AB The p90 ribosomal S6 kinase 2 (RSK2) is a serine/threonine kinase with high expression levels in adipose tissue. Numerous in vitro studies show that RSK2 is activated by a broad number of cellular stimuli and suggest that RSK2 is involved in the regulation of a variety of cellular processes. However, the physiol. role of RSK2 still remains elusive. We therefore generated rsk2 knockout (KO) mice to better understand the function of RSK2 in vivo. Birth wts. of RSK2 KO mice are normal, but the body weight is reduced with age, as compared with wild-type littermates. We found that the difference in body weight was largely caused by a specific loss of white adipose tissue that is accompanied by reduced serum levels of the adipocyte-derived peptide, leptin. KO mice also have impaired glucose tolerance and elevated fasting insulin and glucose levels that are restored following administration of low amts. of leptin, which do not affect food intake. We conclude that RSK2 plays a novel and an important role in regulation of adipose mass in mice and speculate that the reduction in fat tissue may neg. affect insulin sensitivity, as observed in human lipodystrophy, through reduced levels of adipocyte-derived factors, such as leptin.

RE.CNT 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 19 MEDLINE on STN DUPLICATE 3
AN 2002404389 MEDLINE
DN PubMed ID: 12153571
TI Signalling pathways and combinatory effects of insulin and amino acids in isolated rat hepatocytes.
AU Krause Ulrike; Bertrand Luc; Maisin Liliane; Rosa Maria; Hue Louis

CS Hormone and Metabolic Research Unit, Christian de Duve International Institute of Cellular and Molecular Pathology, and University of Louvain Medical School, Brussels, Belgium.
SO European journal of biochemistry / FEBS, (2002 Aug) Vol. 269, No. 15, pp. 3742-50.
Journal code: 0107600. ISSN: 0014-2956.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 200209
ED Entered STN: 3 Aug 2002
Last Updated on STN: 10 Sep 2002
Entered Medline: 9 Sep 2002
AB Liver metabolism is influenced by hormones and nutrients. Amino acids such as glutamine or leucine induce an anabolic response, which resembles that of insulin in muscle and adipose tissue. In this work, the signalling pathways and the effects of insulin were compared to those of glutamine and leucine in isolated hepatocytes from normal and streptozotocin-diabetic rats. Glutamine increased cell volume and induced an anabolic response characterized by an activation of acetyl-CoA carboxylase (ACC), glycogen synthase (GS) and p70 ribosomal S6 kinase (p70S6K), the key enzymes in fatty acid, glycogen and protein synthesis, respectively. The effects of glutamine were independent of insulin and did not share its signalling components. Leucine, which is poorly metabolized by the liver and does not modify cell volume, activated ACC and p70S6K, and exerted a synergistic effect on the glutamine-induced activation of ACC and p70S6K. These amino acids did not affect insulin signalling. Insulin alone had no anabolic effect in hepatocytes, despite the activation of protein kinase B. Nevertheless, it enhanced the activation of ACC and p70S6K induced by leucine. However, insulin injected intravenously activated rat liver p70S6K. In hepatocytes from streptozotocin-diabetic animals, the metabolic responses to the amino acids and insulin were similar to those in normal hepatocytes. We conclude that glutamine, insulin and leucine exert different effects that are mediated by different signalling pathways, although their effects are combinatory. The anabolic effect of insulin in hepatocytes was strictly dependent on the permissive action of leucine.

L4 ANSWER 11 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2002:975077 CAPLUS
DN 138:351652
TI β-Oxidation of free fatty acids is required to maintain translational control of protein synthesis in heart
AU Crozier, Stephen J.; Bolster, Douglas R.; Reiter, Ali K.; Kimball, Scot R.; Jefferson, Leonard S.
CS Department of Cellular and Molecular Physiology, The Pennsylvania State University College of Medicine, Hershey, PA, 17033, USA
SO American Journal of Physiology (2002), 283(6, Pt. 1), E1144-E1150
CODEN: AJPHAP; ISSN: 0002-9513
PB American Physiological Society
DT Journal
LA English
AB The study described herein investigated the role of free fatty acids (FFAs) in the maintenance of protein synthesis in vivo in rat cardiac and skeletal muscle. Suppression of FFA β-oxidation by Me palmoxirate caused a marked reduction in protein synthesis in the heart. The effect on protein synthesis was mediated in part by changes in the function of eukaryotic initiation factors (eIFs) involved in the initiation of mRNA

translation. The guanine nucleotide exchange activity of eIF2B was repressed, phosphorylation of the α-subunit of eIF2 was enhanced, and phosphorylation of eIF4E-binding protein-1 and ribosomal protein S6 kinase was reduced. Similar changes in protein synthesis and translation initiation were not observed in the gastrocnemius following treatment with Me palmoxirate. In heart, repressed β-oxidation of FFA correlated, as demarcated by changes in the ATP/AMP ratio and phosphorylation of AMP-activated kinase, with alterations in the energy status of the tissue. Therefore, the activation state of signal transduction pathways that are responsive to cellular energy stress represents one mechanism whereby translation initiation may be regulated in cardiac muscle.

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 2000:790621 CAPLUS
DN 133:345535
TI Altering ribosomal S6 kinase activity for treatment of obesity related conditions, Coffin-Lowry syndrome and lipodystrophy
IN Bjorbaek, Christian; Goodyear, Laurie J.; Flier, Jeffrey S.
PA Beth Israel Deaconess Medical Center, USA; Joslin Diabetes Center
SO PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000066721	A2	20001109	WO 2000-US11679	20000501
	WO 2000066721	A3	20010705		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 20030158139	A1	20030821	US 2002-261092	20020927
PRAI	US 1999-131762P	P	19990430		
	WO 2000-US11679	A1	20000501		
	US 2001-16692	B1	20011030		

AB Methods and compns. for the treatment of obesity, reducing body weight, body fat, serum leptin levels, and increasing oxygen consumption by altering activity of the ribosomal S6 kinase (RSK2) is disclosed. Use of RSK2 inhibitors, rsk2 antisense oligonucleotides, specifically, is claimed. Methods for screening RSK2 inhibitors as drug candidates for Coffin-Lowry syndrome and lipodystrophy, are described. Determination of phenotypic parameters such as learning capacity, adipose tissue levels, serum leptin levels, glucose sensitivity, body weight, insulin resistance, and diet induced fat gain, are involved. The present invention is further drawn to use of the rsk2 knockout mouse as a model to study and treatment of lipodystrophy and impaired glucose tolerance in mammals. Deletion of the rsk2 gene in mice resulted in reduced body weight, reduced body fat and reduced sensitivity to diet-induced weight gain, as well as lower levels of leptin in the serum of rsk2 deficient mice and lower levels of oxygen consumption, as compared to wild type littermates. Thus,

altering RSK2 activity provides a means for modulating RSK2-mediated signaling and therefore modulating the above described physiol. parameters.

L4 ANSWER 13 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1998:164954 CAPLUS
DN 128:304236
OREF 128:60160h,60161a
TI Mitogen-activated protein kinase and p70 ribosomal protein S6 kinase are not involved in the insulin-dependent stimulation of cAMP phosphodiesterase kinase in rat adipocytes
AU Onuma, Hiroshi; Makino, Hideichi; Osawa, Haruhiko; Suzuki, Yoshifumi; Taira, Masato; Kanatsuka, Azuma; Saito, Yasushi
CS Department of Laboratory Medicine, Ehime University, School of Medicine, Ehime, 791-02, Japan
SO Biochimica et Biophysica Acta, Molecular Cell Research (1998), 1402(2), 197-208
CODEN: BBAMCO; ISSN: 0167-4889
PB Elsevier B.V.
DT Journal
LA English
AB To elucidate the mechanism of anti-lipolytic action of insulin in rat epididymal adipocytes, the authors explored the potential mechanism that might be involved in the hormone-dependent stimulation of cAMP phosphodiesterase (PDE) kinase. PDE kinase was assayed in a cell-free system. Both wortmannin and LY294002, highly specific inhibitors of phosphatidylinositol 3-kinase, almost completely blocked the hormonal effect not only on PDE kinase but also on mitogen-activated protein (MAP) kinase. Neither PD98059, a specific inhibitor of MAP kinase, nor rapamycin, a potent inhibitor of insulin-dependent stimulation of p70 ribosomal protein S6 kinase (p70S6K), had inhibitory effect on that of PDE kinase. These results are consistent with the view that (i) insulin-activated PDE kinase as well as MAP kinase and p70S6K are localized downstream of phosphatidylinositol 3-kinase, (ii) PDE kinase is distinct from either MAP kinase or p70S6K and (iii) PDE kinase does not exist downstream of either MAP kinase or p70S6K. It is suggested that PDE kinase and MAP kinase or p70S6K may be localized in sep. branches of the cascade of insulin action. The branching point of the cascade could be either at or below the level of phosphatidylinositol 3-kinase.
RE.CNT 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1995:313647 CAPLUS
DN 122:72380
OREF 122:13575a,13578a
TI Insulin stimulation of glycogen synthesis and glycogen synthase activity is blocked by wortmannin and rapamycin in 3T3-L1 adipocytes: evidence for the involvement of phosphoinositide 3-kinase and p70 ribosomal protein-S6 kinase
AU Shepherd, Peter R.; Nave, Barbara T.; Siddle, Kenneth
CS Addenbrooke's Hospital, University of Cambridge, Cambridge, CB2 2QR, UK
SO Biochemical Journal (1995), 305(1), 25-8
CODEN: BIJOAK; ISSN: 0264-6021
PB Portland Press
DT Journal
LA English
AB The authors have investigated the involvement of phosphoinositide (PI) 3-kinase and p70 ribosomal protein-S6 kinase (p70s6k) in mediating insulin stimulation of glycogen synthesis in 3T3-L1

adipocytes using specific inhibitors. Wortmannin inhibited PI 3-kinase activity (IC50 ≈ 10 nM), inhibition being complete at 100 nM. Wortmannin (100 nM) completely blocked the ability of insulin to activate glycogen synthase in 3T3-L1 adipocytes and the ability of insulin to stimulate glucose incorporation into glycogen in 3T3-L1 fibroblasts. Rapamycin, which blocks insulin-stimulated activation of p70s6k, decreased insulin activation of glycogen synthase in a dose-dependent manner (IC50 .apprx. 0.8 ng/mL), with a maximum .apprx.75% inhibition of insulin's stimulatory effect. Rapamycin inhibited insulin-stimulated glucose incorporation into glycogen to a similar extent and with similar dose-dependency, while having no effect on insulin-stimulated glucose transport. The authors conclude that PI 3-kinase and p70s6k are involved in the signaling pathways by which insulin stimulates glycogen synthase in 3T3-L1 adipocytes.

L4 ANSWER 15 OF 19 MEDLINE on STN DUPLICATE 4
AN 1988029451 MEDLINE
DN PubMed ID: 2822412
TI Activation of a ribosomal protein S6 kinase in mouse fibroblasts during infection with herpesvirus.
AU Jakubowicz T; Leader D P
CS Department of Biochemistry, University of Glasgow, Scotland.
SO European journal of biochemistry / FEBS, (1987 Oct 15) Vol. 168, No. 2, pp. 371-6.
Journal code: 0107600. ISSN: 0014-2956.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 198712
ED Entered STN: 5 Mar 1990
Last Updated on STN: 5 Mar 1990
Entered Medline: 8 Dec 1987
AB If confluent fibroblasts are infected with the swine alpha-herpes virus, pseudorabies virus, ribosomal protein S6 becomes phosphorylated after a lag of approximately 2 h. When cell-free extracts were prepared from such cells in the presence of glycerol 2-phosphate and EGTA, a ribosomal protein S6 kinase activity was found to appear at approximately the same time as the phosphorylation in vivo. This protein kinase was similar to that activated in the same cells by replenishing the nutrient medium, and in other quiescent cells by the action of growth factors and mitogens. It was distinct from the previously described pseudorabies virus protein kinase, which is unique to infected cells. When medium from cells infected with pseudorabies virus was freed of virus and added to confluent fibroblasts, rapid activation of the ribosomal protein S6 kinase activity occurred. A similar, although more limited, effect could be seen when the pH of the medium was increased. These results suggest that the phosphorylation of ribosomal protein S6 in cells infected with herpes virus is a consequence of the production of a factor which initiates the metabolic programme for cellular growth. The possible function of this effect in the infective strategy of herpes viruses is discussed in relation to requirements for the replication of viral DNA.

L4 ANSWER 16 OF 19 MEDLINE on STN DUPLICATE 5
AN 1987161902 MEDLINE
DN PubMed ID: 3030755
TI Induction, partial purification and characterization of a hamster fibroblast protein kinase activity that phosphorylates ribosomal protein S6.

AU Jakubowicz T; Leader D P
SO European journal of biochemistry / FEBS, (1987 Apr 1) Vol. 164, No. 1, pp. 83-8.
Journal code: 0107600. ISSN: 0014-2956.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LA English
FS Priority Journals
EM 198705
ED Entered STN: 3 Mar 1990
Last Updated on STN: 3 Mar 1990
Entered Medline: 15 May 1987
AB When BHK cells were grown to confluence and the growth medium replenished, there was a large and rapid increase in the phosphorylation of ribosomal protein S6. In postribosomal extracts of these cells, prepared in the presence of glycerol 2-phosphate and EGTA, a ribosomal protein S6 kinase was detected. The increase in activity of this protein kinase broadly reflected the increase in phosphorylation of ribosomal protein S6 observed in vivo. This ribosomal protein S6 kinase activity was substantially purified by a combination of phosphocellulose, DEAE-cellulose, Mono Q and heparin-Sepharose chromatography, and some of its characteristics were examined. When the products of phosphorylation of 40S ribosomal subunits by purified enzyme in vitro were analysed using two-dimensional gel electrophoresis, monophosphorylated and diphosphorylated forms of ribosomal protein S6 were observed to be the predominant radioactively labelled species.

L4 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1986:586462 CAPLUS
DN 105:186462
OREF 105:30009a,30012a
TI An insulin-stimulated ribosomal protein S6 kinase in 3T3-L1 cells
AU Cobb, Melanie H.
CS Health Sci. Cent., Univ. Texas, Dallas, TX, 75235, USA
SO Journal of Biological Chemistry (1986), 261(28), 12994-9
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB A protein kinase that is stimulated 2-10-fold by insulin and that phosphorylates ribosomal protein S6 was characterized in 3T3-L1 cells. The detection of this activity in the 100,000-g supernatant was facilitated by the presence of β-glycerol phosphate or vanadate in the homogenization buffer. The activity was purified 55-fold by chromatog. on DEAE-cellulose and phosphocellulose. The resulting specific activity is 584 pmol/min/mg of protein. DEAE-cellulose chromatog. followed by gel filtration on Ultrogel AcA54 or by glycerol gradient centrifugation suggests that the protein has a mol. mass of 60,000-70,000 daltons. Mg2+, and to a lesser extent Mn2+, will support phosphorylation of S6 by the enzyme. No proteins tested other than ribosomal protein S6 are phosphorylated. Based on its chromatog. properties and substrate specificity, the enzyme appears to be distinct from several other protein kinases that are known to phosphorylate ribosomal protein S6 in vitro. The complete characterization and purification of this enzyme may be essential to the elucidation of the mechanism of regulation of S6 phosphorylation by insulin.

L4 ANSWER 18 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1986:473064 CAPLUS

DN 105:73064
OREF 105:11745a,11748a
TI A similar ribosomal protein S6 kinase activity is found in insulin-treated 3T3-L1 cells and chick embryo fibroblasts transformed by Rous sarcoma virus
AU Cobb, Melanie H.; Burr, John G.; Linder, Maurine E.; Gray, Teri B.; Gregory, Jill S.
CS Health Sci. Cent., Univ. Texas, Dallas, TX, 75235, USA
SO Biochemical and Biophysical Research Communications (1986), 137(2), 702-8
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB Insulin [9004-10-8] and transformation by Rous sarcoma virus stimulated the phosphorylation of ribosomal protein S6 of 3T3-L1 cells or chick embryo fibroblasts. Soluble fractions containing activated S6 protein kinase from insulin-treated cells and from transformed chick embryo fibroblasts were compared. Based on several characteristics notably elution from DEAE-cellulose and sedimentation in glycerol gradients, these two S6 protein kinase activities appear to be similar enzymes. Thus insulin and retroviral transformation may activate the same enzyme to regulate the phosphorylation state of S6.

L4 ANSWER 19 OF 19 CAPLUS COPYRIGHT 2009 ACS on STN
AN 1983:590420 CAPLUS
DN 99:190420
OREF 99:29231a,29234a
TI Description of a protein kinase derived from insulin-treated 3T3-L1 cells that catalyzes the phosphorylation of ribosomal protein S6 and casein
AU Cobb, Melanie H.; Rosen, Ora M.
CS Dep. Mol. Pharmacol., Albert Einstein Coll. Med., Bronx, NY, 10461, USA
SO Journal of Biological Chemistry (1983), 258(20), 12472-81
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Particulate prepns. from insulin-treated 3T3-L1 cells retain the enhanced ability to incorporate 32P from [γ-32P]ATP into ribosomal protein S6. A cAMP-independent protein kinase that phosphorylates S6 and casein and that may be involved in the increase in S6 phosphorylation produced by insulin was isolated based upon the observation that there is 1.5-3.0-fold higher activity in particulate prepns. derived from insulin-treated cells than there is in comparable prepns. from control cells. The enzyme activity was purified 2071-fold by KCl extraction, phosphocellulose chromatog., and gel filtration. The S6-phosphorylating activity was also characterized by its behavior on casein-Sepharose and DEAE-cellulose chromatog. and its sedimentation in glycerol gradients. None of these procedures resolved the S6 and casein kinase activities. Some of the properties of this kinase, including a mol. weight of .apprx.35,000, inhibition by F- or phosphate, chromatog. on DEAE-cellulose and phosphocellulose, and insensitivity to inhibition by GTP, are similar to those of a previously described enzyme, casein kinase I.